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(54) Title: NUTRITIONAL COMPOSITION FOR IMPROVED COGNITIVE PERFORMANCE

(57) Abstract

A nutritional composition for the improvement of cognitive performance comprising caffeine, choline, gamma aminobutyric acid, L-phenylalanine, and taurine in amounts sufficient to result in a measurable improvement in at least one physiologic effect associated with improved cognitive performance, together with methods for use of the composition. The composition avoids the use of stimulant medications, antidepressants, and/or anxiolytics, while relying on active ingredients which have been demonstrated to have only minimal side effects or negative indications.

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Description

Nutritional Composition For Improved Cognitive Performance

Technical Field

The present invention relates to nutritional compositions and, more particularly, to nutritional compositions which can improve various parameters of cognitive performance.

Background of the Invention

There are numerous parameters which have an impact in a comprehensive evaluation of cognitive performance. These parameters can be influenced by lifestyle, e.g. amount of sleep, number of distractions, or by biochemical or other organic influences.

For example, attention-deficit hyperactivity disorder (ADHD) affects a significant number of children, adolescents, and adults and has gained increasing attention over the last decade. The disorder is characterized by inattention (distractibility) or hyperactivity, or a combination thereof, and when severe, inhibits the normal developmental learning processes. Concomitant difficulties in the areas of socialization and behavior frequently are seen as well. Current treatment modalities include administration of stimulant medications, antidepressants, and anxiolytics, with stimulants being the most frequently prescribed. Among the stimulant medications most widely utilized are methylphenidate (commonly prescribed as Ritalin®), pemoline, and dexamphetamine; currently, methylphenidate exists as the treatment of choice by most physicians. However, there are potential side-effects of methylphenidate, including appetite suppression and, according to some studies, negative indications such as growth retardation with long-term use (Schachar, R.J. *et al.*, *J. Am. Acad. Child Adolesc. Psychiatry* 36(6):754-63 (1997); Tannock, R. and R. Schachar, *J. Abnorm. Child Psychol.* 23(2):235-66 (1995); American Academy of Pediatrics Committee on Children with Disabilities and Committee of Drugs. *Pediatrics* 99(6):922, 923 (1997); Pataki, C.S. *et al.*, *J. Am. Acad. Child Adolesc. Psychiatry* 32(5):1065-72 (1993);

Rapport, M.D. *et al.*, *Behav. Modif.* **20(4)**:428-30 (1996); Gilberg, C *et al.*, *Arch. Gen. Psychiatry* **54(9)**:857-64 (1997); Pelham, W.E., *et al.*, *Exp. Clin. Psychopharmacol.* **5(1)**:3-13 (1997)).

In recent years nutritional products have become available as safer, yet promising, alternative treatments. Nutritional supplements, such as caffeine (Sawynok, J. *Drugs* **49(1)**:37-50 (1995)), choline (Shronts, E.P., *J. Am. Diet Assoc.* **97(6)**:639-46 (1997); Buchman, A.L. *Am. J. Clin. Nutr.* **65(2)**:574-5 (1997); Emmert, J.L. *et al.*, *J. Anim. Sci.* **74(11)**:2738-44 (1996); Stoll, A.L. *et al.*, *Biol. Psychiatry* **40(5)**:382-8 (1996); Freeman, J.J., *Life Sci.* **58(22)**:1921-7 (1996); Chohen, B.M. *et al.*, JAMA **274(11)**:902-7 (1995); Woodbury M.M. and M.A. Woodbury, *J. Am. Coll. Nutr.* **12(3)**:239-45 (1993); Loffelholz, K. *et al.*, *Prog. Brain Res.* **98**:197-200 (1993)), gamma aminobutyric acid (Nasybullina, N.M. *et al.*, *Eksp. Klin. Farmakol.* **60(2)**:58-61 (1997); Vauzelle-Kervroedan, F. *et al.*, *Br. J. Pharmacol.* **42(6)**:779-81 (1996), carnitine (Beversdorf, D. *et al.*, *J. Neurol. Neurosurg. Psychiatry* **61(2)**:211 (1996); Sahajwall, C.G. *et al.*, *J. Pharm. Sci.* **84(5)**:634-9 (1995); Sahajwall, C.G. *et al.*, *J. Pharm. Sci.* **84(5)**:627-33 (1995); Plioplys, A.V. *et al.*, *No To Hattatsu [Brain and Development]* **16(2)**:146-9 (1994); Plioplys, A.V. and I. Kasnicka, *South. Med. J.* **86(12)**:1411-2 (1993); Shapira, Y. *et al.*, *Pediatr. Neurol.* 9(1):35-8 (1993)), and pyridoxine (vitamin B-6) (Z. *Ernahrungswiss* **35(4)**:309-17 (1996)) have been shown to improve cognitive performance and psycho-motor function in hypotonic children, and psycho-motor retardation in hyperkinetic children.

Accordingly, it is considered desirable to provide a nutritional composition for the improvement of cognitive performance which will avoid the use of stimulant medications, antidepressants, and/or anxiolytics, while relying on active ingredients which have been demonstrated to have only minimal side effects or negative indications.

Disclosure of the Invention

The present invention provides a nutritional composition for the improvement of cognitive performance which avoids the use of stimulant medications, antidepressants, and/or anxiolytics, while relying on active ingredients which have been demonstrated to have only minimal side effects or negative indications.

In one aspect, the invention provides a composition for improvement of cognitive performance comprising caffeine, choline, gamma aminobutyric acid, L-phenylalanine, and taurine in amounts sufficient to result in a measurable improvement in at least one physiologic effect associated with improved cognitive performance.

A further aspect of the invention provides methods for using the present composition for treating a mammal for inducing therein a beneficial effect on at least one physiologic parameter associated with improved cognitive performance comprising administering to a mammal a composition of the invention in an amount sufficient to result in a measurable improvement in said physiological parameter.

Detailed Description of the Invention

The present invention provides a nutritional composition for the improvement of cognitive performance which avoids the use of stimulant medications, antidepressants, and/or anxiolytics, while relying on active ingredients which have been demonstrated to have only minimal side effects or negative indications.

In one aspect, the invention provides a composition for improvement of cognitive performance comprising caffeine, choline, gamma aminobutyric acid, L-phenylalanine, and taurine in amounts sufficient to result in a measurable improvement in at least one physiologic effect associated with improved cognitive performance.

Dietary fluctuations in nutrient availability are factors in the regulation of brain function. The prevailing view once was that brain biochemistry and function were influenced by diet only when biochemical and clinical evidence of nutrient deficiency was present. More recently it appears clear that the brain is sensitive and responsive to diet composition. Data have shown that variation in vitamin and mineral nutrient intakes over ranges that are considered to maintain normal nutritional status may impact on brain biochemistry, owing in part to their many coenzyme roles. Furthermore, the synthesis of at least five brain neurotransmitters, namely serotonin, the catecholamines, acetylcholine, histamine, and glycine, responds to dietary fluctuations in availability of their nutrient precursors, namely tryptophan, tyrosine, choline, histidine, and threonine, respectively. Not only are these biochemical events altered by normal variations in diet composition, but evidence now exists to show that the brain uses this information to regulate many functions (Anderson, G. H. and J. L. Johnston, *Can. J. Physiol. Pharmacol.* 61(3): 271-81 (1983)).

Primary Neuroactive Components

1. Caffeine

Caffeine (3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) is found naturally in coffee beans, tea leaves, maté leaves, guarana paste and cola nuts, among other botanical sources, and is obtained industrially as a by-product of de-caffeinated coffee. It is a commonly-known CNS stimulant, and has found use in veterinary medicine as a cardiac and respiratory stimulant and as a diuretic. Caffeine has long been known to have effects on the physiological state of dietary consumers, but little has been done to investigate the efficacy of caffeine in the improvement of physiologic parameters of cognitive performance and particularly in the treatment of ADHD. It has been reported that high caffeine users performed more poorly than other groups on verbal reasoning tasks (Mitchell, P. J. and J. R. Redman, *Psychopharmacology* **109**(1-2):121-126 (1992)), and conversely, that caffeine consumption can be beneficial for cognitive functioning (Riedel, W. *et al.*, *Psychopharmacology* **122**(2):158-68 (1995).

It has often been pointed out that caffeine is the most widely "used" psychoactive substance in the world, and accordingly, there is a very large amount of research available on the effects of caffeine on body and mind. In particular, a psychostimulant action of caffeine is generally accepted as well established: For example, caffeine has been found to quicken reaction time and enhance vigilance performance, and to increase self-rated alertness and improve mood. There is, however, a real difficulty in determining the net effects of caffeine. In a typical experiment the subjects have a history of regular caffeine consumption, and they are tested on caffeine and a placebo after a period of caffeine deprivation (often overnight). The problem with relying solely on this approach is that it leaves open the question as to whether the results obtained are due to beneficial effects of caffeine or to deleterious effects of caffeine deprivation (Rogers, P. J. and C. Dernoncourt, *Pharmacol. Biochem. Behav.* 59(4):1039-45 (1998)).

In the nutritional composition of the present invention, it has been found that caffeine when administered together with selected nutritional components, provides a

significant benefit in the improvement of cognitive performance. Typically, a caffeine component in the range of approximately 60 to 180 milligrams per dose will prove to be useful, more commonly in the range of approximately 96 to 144 milligrams per dose, and optimally in the range of approximately 120 milligrams per dose will provide the desired benefits.

2. Choline

Choline (2-Hydroxy-N,N,N-trimethylethanaminium) is a basic component of lecithin, and is found in many plants and animal organs, e.g bile, brain, yolk of eggs, and the like. It is usually made synthetically from trimethylamine and ethylene chlorohydrin or ethylene oxide. It is known as the biochemical precursor to acetylcholine, an important neurotransmitter in mammals, as well as membrane phospholipids.

Cholinergic neurons are unique among cells since they alone utilize choline not only as a component of major membrane phospholipids, such as phosphatidylcholine (Ptd-Cho), but also as a precursor of their neurotransmitter acetylcholine (AcCho) (Blusztajn, J. K. *et al.*, *Proc. Natl. Acad. Sci. USA* 84(15):5474-7 (1987)). A prolonged utilization of choline liberated from PC, for ACh production, without adequate resynthesis of this lipid, might result in a net loss of the phosphatide followed by an impairment of membrane function and loss of cellular viability (Blusztajn, J. K. *et al.*, *J. Neural. Transm. Suppl.* 24:247-59 (1987)). However, it is not clear that administration of dietary choline would produce beneficial improvements in cognitive performance in individuals not manifesting pathological conditions.

In one report, phosphatidylcholine treatment did not affect memory or acetylcholine concentrations of normal mice in spite of a great increase in choline concentrations in three brain regions, but administration of phosphatidylcholine to mice with dementia increased brain acetylcholine concentration and improved memory (Chung, S. Y. et al., *J. Nutrition* 125(6):1484-9 (1995)).

Thus, despite the usefulness of such precursors as therapeutic agents for the treatment of selected disease states, wherein the disease is related to reduced release of transmitter, it has not been clear that they would provide improvement in cognitive performance for normal individuals.

In the nutritional composition of the present invention, it has been found that choline when administered together with selected nutritional components, provides a significant benefit in the improvement of cognitive performance. Typically, a choline component in the range of approximately 250 to 750 milligrams per dose will prove to be useful, more commonly in the range of approximately 400 to 600 milligrams per dose, and optimally in the range of approximately 500 milligrams per dose will provide the desired benefits.

Gamma Aminobutyric Acid

Gamma aminobutyric acid (4-Aminobutanoic acid, γ-amino-*n*-butyric acid, GABA) is a non-protein amino acid that functions as a neurotransmitter. It is generally prepared synthetically from succinimide, or numerous other substrates, and has been used as an antihypertensive.

In the nutritional composition of the present invention, it has been found that GABA when administered together with selected nutritional components, provides a significant benefit in the improvement of cognitive performance. Typically, a GABA component in the range of approximately 25 to 75 milligrams per dose will prove to be useful, more commonly in the range of approximately 40 to 60 milligrams per dose, and optimally in the range of approximately 50 milligrams per dose will provide the desired benefits.

L-Phenylalanine

L-Phenylalanine (β-Phenylalanine) is a protein amino acid classified as an essential component of human nutrition (i.e. it is not synthesized by the human body in sufficient quantities to meet metabolic needs) with a high recommended daily intake. It

is a major component of whole egg and skim milk, and is isolated commercially from ovalbumin, zein, and fibrin.

In the nutritional composition of the present invention, it has been found that L-Phenylalanine when administered together with selected nutritional components, provides a significant benefit in the improvement of cognitive performance. Typically, a L-Phenylalanine component in the range of approximately 250 to 750 milligrams per dose will prove to be useful, more commonly in the range of approximately 400 to 600 milligrams per dose, and optimally in the range of approximately 500 milligrams per dose will provide the desired benefits.

Taurine

Taurine (2-aminoethanesulfonic acid) is a non-protein amino acid classified as a conditionally essential component of human nutrition, important in early mammalian development. It conjugates bile acids, and is present in most milk (but only minimally in bovine milk), extracts of oxen, shark blood, mussels, and oysters. It is isolated commercially from ox bile or the large muscle of abalone (*Haliotis* spp.).

Taurine is well known for its role in bile salt synthesis, and is also involved in a number of crucial physiological processes including modulation of calcium flux and neuronal excitability, osmoregulation, detoxification, and membrane stabilization. With the exception of cow's milk, taurine is widely distributed in foods from many animal, but not plant, sources. Although taurine is synthesized from sulfur-containing amino acids, concern has been expressed about the adequacy of endogenous sources, especially in neonates. Accordingly, proprietary milk formulas are now supplemented with taurine. Retinal dysfunction occurs in taurine-deficient animals. A milder form of this condition has been observed in children on long-term total parenteral nutrition. Preliminary evidence suggests a possible role for taurine administration in congestive heart disease, acute hepatitis, cystic fibrosis, and myotonia (Kendler, B. S. *Prev. Med.* 18(1):79-100 (1989)).

In the nutritional composition of the present invention, it has been found that taurine when administered together with selected nutritional components, provides a

significant benefit in the improvement of cognitive performance. Typically, a taurine component in the range of approximately 100 to 300 milligrams per dose will prove to be useful, more commonly in the range of approximately 160 to 240 milligrams per dose, and optimally in the range of approximately 200 milligrams per dose will provide the desired benefits.

Secondary Neuroactive Components

In addition to the benefits realized through the use of nutritional compositions containing the above-noted primary components, additional benefits are obtained through the use of compositions which contain certain secondary neuroactive components, including L-carnitine, L-glycine, ribonucleic acid (RNA), and ubiquinone. Typically, in the nutritional composition of the present invention, it has been found that a significant additional benefit in the improvement of cognitive performance will be obtained when such secondary components are included in the following approximate ranges:

L-carnitine, commonly in the range of approximately 5 to 15 milligrams per dose, and optimally in the range of approximately 10 milligrams per dose;

L-glycine, commonly in the range of approximately 50 to 150 milligrams per dose, and optimally in the range of approximately 100 milligrams per dose;

Ribonucleic acid (RNA), commonly in the range of approximately 1 to 3 milligrams per dose, and optimally in the range of approximately 2 milligrams per dose;

Ubiquinone, commonly in the range of approximately 50 to 150 micrograms per dose, and optimally in the range of approximately 100 micrograms per dose;

will provide the desired benefits.

Additional Nutritional Components

Certain additional nutritional components, although not known to be clearly neuroactive when administered individually, will also provide benefits when

administered to mammals in a complete nutritional composition. Such additional components will include, for example, fructose, maltodextrin, citric acid, ascorbic acid, natural flavor, calcium pantothenate, Vitamin A (beta carotene, palmitate), niacinamide, Vitamin E succinate, acesulfame, niacin, pyridoxine hydrochloride, zinc mono-methionine, riboflavin, thiamin hydrochloride, copper amino acid chelate, chromium polynicotinate, and cyanocobalamin.

Formulation and Dosage of Compositions

In practicing the method of the present invention, the nutritional composition will be administered to a mammalian host in need of such improvement at a therapeutically effective dosage level. The compositions of the present invention will desirably be administered orally, in the form of capsules, tablets or suspensions. Alternatively, the compositions can be administered by any other means considered desirable.

The lowest effective dosage levels can be determined routinely by initiating treatment at higher dosage levels and reducing the dosage level until improvement of cognitive performance is no longer obtained. Generally, therapeutic dosage levels will range from about 0.01 to 100 milligrams per kilogram of host body weight. As a starting point, typically 1g to 1.5g of the present composition is given three times a day. The composition can also be administered at 2.5 to 6000 milligrams per kilogram of body weight. Improvement is generally detectable within a brief period after administration, often in less than one hour. The amount necessary to achieve therapeutic effect for a particular individual will depend upon a number of factors such as body weight and age of the individual.

It is not intended that the present invention be limited by the particular nature of the preparation. For example, such compositions can be provided together with pharmaceutically acceptable and physiologically tolerable liquid, gel or solid carriers, diluents, adjuvents and excipients. These therapeutic preparations can be administered to mammals, both for veterinary use, such as with domestic animals, and clinical use in humans in a manner similar to other therapeutic agents. In general, the dosage

required for therapeutic efficacy will vary according to the type of use and mode of administration, as well as the particularized requirements of individual hosts.

Such compositions are typically prepared for oral administration, either as dry formulations such as dry powders, encapsulated or free, or as liquid solutions or suspensions. Oral formulations (e.g. for gastrointestinal absorption) often includes such normally employed additives such as binders, fillers, carriers, preservatives, stabilizing agents, emulsifiers, buffers and excipients such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained-release formulations, or powders, and typically contain 1% to 95% of active ingredient, preferably 2% to 70%. The compositions of the present invention are also capable of being prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared.

The compounds of the present invention are often mixed with diluents or excipients which are physiologically tolerable and compatible. Suitable diluents and excipients are, for example, water, saline, dextrose, glycerol, or the like, and combinations thereof. In addition, if desired, the compositions may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, stabilizing or pH buffering agents.

Additional formulations which are suitable for other modes of administration, such as topical administration, includes salves, tinctures, creams, lotions and, in some cases, suppositories. For salves and creams, traditional binders, carriers and excipients may include, for example, polyalkylene glycols or triglycerides.

Testing Methodologies

1. Subjects

Criteria for subjects for evaluation of the improvement of cognitive performance are children ages 6-17 with a known diagnosis of ADHD, who are currently followed by a physician and on medication with methylphenidate. Subjects are excluded if they are abnormally sensitive to caffeine or phenylalanine or if they have any condition that would preclude them from consideration as participants.

2. Procedure

A sufficient number of eligible subjects are evaluated so as to provide statistical significance for the results. The subjects are randomly assigned to two treatment groups: methylphenidate and nutritional composition. All are evaluated twice; once when given the treatment, the other when given a placebo. The order of placebo or treatment administration is a function of the random assignment and blinding process. Each evaluation consisted of 1) a Test of Variables of Attention (T.O.V.A.), a computerized continuous performance test, and 2) a neurofeedback (NFB) session. The T.O.V.A. evaluation measures accuracy in identifying and responding to the visual stimuli presented, the speed of the response to the visual stimuli and the variability of the response to the visual stimuli. The NFB consists of a 3-minute monitoring session to measure theta and beta wave response.

Subjects and care givers are interviewed to obtain informed consent, to ascertain sensitivities to caffeine and/or phenylalanine, and to schedule appointments for the evaluations. Because of the 1) established rapid mechanism of action for stimulant medication (peak efficacy rate for methylphenidate is 1.9 hours), 2) typical weekend and holiday breaks prescribed by physicians, and 3) the evidence in previous research regarding similar rapid efficacy for caffeine (Sawynok, J. *Drugs* **49**(1):37-50 (1995)), the study relied on a 24-hour washout period and a brief (2 hour) period between treatment administrations and assessments.

Methylphenidate (10mg) treatment dosages are converted to powder form and mixed in a beverage powder similar in taste and consistency to the nutritional

composition beverage mixture. In additon, a beverage without any active ingredients is used as a placebo. Two hours prior to each of the two evaluative sessions, subjects are given one of the two treatment compositions or the placebo. The subjects are then either to stay in the Center (movies, books, are provided as activities) or are allowed to leave with their parents/guardians to return at the time of the actual evaluation. Just as with typical methylphenidate treatment, subjects are allowed to conduct regular activities. Neither subjects nor clinicians/investigators knew whether the composition contained methylphenidate, the nutritional mixture or placebo.

3. Measures

Continuous Performance Test (CPT)

The Test of Variables of Attention (T.O.V.A.) is an individually administered and computerized test developed to assess attention and impulse control in normal and clinical populations. It can be used in conjunction with other information gathering tools or diagnostic tests in neuropsychological or psychological evaluations. The T.O.V.A. was developed to measure attentional and impulse control processes in four areas: 1) inattention, or omissions; 2) impulse control, or commissions; 3) response time; and 4) response time variability. T.O.V.A. scores have shown sensitivity to and reliable improvment with CNS stimulant treatment.

During the T.O.V.A., the visual stimuli presented are two easily discriminated geometric pictures centered on the computer screen. During the test itself, one of the two stimuli is presented for 100msec every two seconds. The designated target is presented 22.5% (n=72) of the trials during the first half of the test (stimulus infrequent condition) and presented 77.5% (n=252) of the trials during the second half (stimulus frequent condition). The task is for the subject to respond to the appropriate target as soon as possible. The varying target-nontarget ratio allows for the examination of the effects of differing response demands on inattention and impulsivity. The test software automatically records the subject's responses, nonresponses, and

reaction times calculating raw scores and percentages free from calculation errors of the examiner.

Variables

Omissions. *Errors of Omission* occur when the subject does not respond to the designated target; that is, the subject omits pressing the button when a target is presented. The omission score is a result of the subject's error of omission and is measured as a ratio of the subject's correct responses to targets to the actual number of targets presented minus the number of anticipatory responses towards targets. Omission scores are presented as percentages and are considered to be a measure of inattention.

Commissions. *Errors of Commission* occur when the subject fails to inhibit responding and incorrectly responds to a nontarget; that is, the subject presses the button when a nontarget is presented. The commission score is a result of the subject's errors of commission and is measured as a ratio of the subject's incorrect responses to nontargets to the actual number of nontargets presented minus the number of anticipatory responses towards nontargets. Commission scores are presented as percentages and are considered to be a measure of impulsivity or disinhibition.

Response Time. *Response Time* is the measure of processing time it takes to respond correctly to a target. It is the electronic measure of time from when a target is presented to when the microswitch is pressed by the subject. Response Time score is the average of the (correct) response times, in which the sum of all correct response times divided by the number of targets and is reported in milliseconds for each quarter, half and total.

Response Time Variability. *Variability* is a measure of the subject's response time variance or inconsistency in response times. The Response Time Variability score is

reported as the standard deviation of the mean correct response times. It is formulated based upon the subject's correct target response times. The variability reflects the variance of the subject's correct target response times for each quarter, half and for total.

T.O.V.A. results are compared to the normal same-gender, same-age, and average IQ group and are reported in z-scores (mean = 0) and standard scores (mean = 100) on four indices: omission, commission, response time, and variability of response. A z-score indicates the extent of a problem. The more negative z-score, the greater the problem. Conversely, a more positive z-score indicates a better than average performance. Normal range for z-scores is -1.00 to +1.00. Normal range for standard scores is 85 to 115 with a mean of 100 and standard deviation of 15. The T.O.V.A. is administered at each of the two evaluation sessions.

Electrophysiological Measures-Neurofeedback

The electrical activity of the brain is measured in two ways. The first is in frequency or cycles per second. On most electroencephalographs the range of freqencies recorded is limited to from 2 to 32 hertz (hz), or cycles per second. The second measurement is the amplitude which is reported in microvolts (v). Instrumentation used for the neurofeedback measures is a FOCUS 1000 Instrumentation system utilizing a 266Mhz Pentium II cpu capable of recording EMG, EGR, EEG, HR, and Temperature readings.

Beta activity occurs within the range of 14-32 hertz and is usually associated with an external focus or with focused, directed thinking. Theta activity occurs within the range of 4-8 hertz and is usually associated with an internal focus or with activity such as dreaming, reverie, and meditation.

Much evidence exists indicating that the slow EEG pattern found in the central and frontal cortex in most individuals with ADHD -- particularly with the inattentive form of ADHD -- is a reflection of a decreased metabolism, blood flow, and oxygen utilization. This altered EEG activity may also indirectly represent altered

neurotransmitter functions in these areas. Research has shown that individuals of the inattentive type specifically showed increased slow activity in central and in frontal locations with decreased low and high beta in posterior cortical regions. Statistically significant group differences in terms of increased theta and decreased beta activity are also found in these patients (Mann, C.A. *et al.*, *Pediatr. Neurol.* 8:30-36 (1992).

Studies showing statistically significant decreases in the microvolt levels of theta also showed a significant improvement in T.O.V.A. scores as compared with those individuals who showed no significant decrease in theta activity (Lubar, J.F. *et al.*, *Appl. Psychophysiol. Biofeedback* 20:83-99 (1995). This data provides direct evidence that there is a relationship between the ability to change EEG and the ability to perform better on an objective and highly important measure of attentiveness.

Data Analysis

Performance by the two treatment groups (nutritional composition, methylphenidate) on each of the T.O.V.A. measures and during the neurofeedback monitoring session is analyzed. All analyses are repeated measures analyses of variance (ANOVAs) with treatment group as the between-subjects factor and trial (treatment vs. placebo) as the within-subjects factor. Significant main effects are analyzed with Tukey HSD post hoc pairwise comparisons.

The following examples serve to illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof.

Experimental

In the experimental disclosure which follows, all weights are given in grams (g), milligrams (mg), micrograms (μg), nanograms (ng), or picograms (pg), all amounts are given in moles (mol), millimoles (mmol), micromoles (μmol), nanomoles (nmol), picomoles (pmol), or femtomoles (fmol), all concentrations are given as percent by volume (%), proportion by volume (v:v), molar (M), millimolar (mM), micromolar (μM), nanomolar (nM), picomolar (pM), femtomolar (fM), or normal (N), all volumes are given in liters (L), milliliters (mL), or microliters (μL), and linear measurements are given in millimeters (mm), or nanometers (nm) unless otherwise indicated.

The following examples demonstrate the practice of the present invention in improving cognitive performance. As a representative example, cognitive performance can be improved in ameliorating certain of the manifestations of attention deficit hyperactivity disorder (ADHD).

Example 1

A nutritional composition in accordance with the present invention is formulated as follows: A nutritional beverage mix which contains naturally-occurring nutrients provided by AdvoCare, Int. as SPARK™. This product includes selected neuroactive ingredients include caffeine (120mg), choline (500mg), gamma aminobutyric acid (GABA) (50mg), L-phenylalanine (500mg), taurine (200mg), L-carnitine (10mg), L-glycine (100mg), RNA (2mg), and ubiquinone (100μg). In addition, the following ingredients are included as minor components: Fructose, maltodextrin, citric acid, ascorbic acid, natural flavor, calcium pantothenate, Vitamin A (beta carotene, palmitate), niacinamide, Vitamin E succinate, acesulfame, niacin, pyridoxine hydrochloride, zinc mono-methionine, riboflavin, thiamin hydrochloride, copper amino acid chelate, chromium polynicotinate, and cyanocobalamin.

This nutritional composition was developed to reduce the negative manifestations of ADHD, such as inattentiveness and distractibility, as measured empirically by a neuropsychological continuous performance test and electrophysiological brain wave measures.

Procedure

Methylphenidate treatment dosages (10mg) are converted to powder form and mixed in a beverage powder similar in taste and consistency to the nutritional composition beverage mixture. In addition, a beverage without any active ingredients is used as a placebo. Two hours prior to each of the two evaluative sessions, subjects are given one of the two treatment compositions or the placebo. As with typical methylphenidate treatment, subjects are allowed to conduct regular activities until the evaluation begins.

Results

T.O.V.A. Measures -Omissions

The treatment groups did not differ reliably on first half, second half, or total omissions, $p > .05$. Mean scores decreased on the placebo administration across all groups $F(5, 285) = 20.85$, $p < .0001$. Tukey HSD comparisons revealed significant differences between treatment and placebo on each of the omission measures, $p < .0001$. Table 1 provides means and standard deviations for the T.O.V.A. omission measures. The interaction of group and trial is not significant, $p > .05$.

T.O.V.A. Measures -Commission

All effects are nonsignificant for first half, second half, and total commissions, $p > .05$. See Table 2 for summary statistics for the T.O.V.A. commission measures.

T.O.V.A. Measures -Response Time

Nutritional composition and methylphenidate are not significantly different across response time measures, $p > .05$. Mean performance at treatment is significantly higher than placebo for all groups, $F(5, 285) = 39.78$, $p < .0001$. The degree of change in response time from treatment to placebo for each group is significant. Tukey post hoc analyses indicate this difference is reliable across first half, second half, and total response times, $p < .0001$. The group x trial interaction is not significant. Means

and standard deviations for first half, second half, and total response time are presented in Table 3.

T.O.V.A. Measures -Response Time Variability

The main effect for groups is not significant for response variability, $p > .05$. Mean response variability decreased from treatment to placebo administration for all groups, $F (5, 285) = 25.45$, $p < .0001$. Tukey tests revealed significant differences between treatment and placebo for each of the response variability measures, $p < .0001$. Means and standard deviations for each group are presented in Table 4. No evidence is found for a group x trial interaction, $p > .05$.

Electrophysiological Measures - Theta & Beta waves (Hz)

All effects for theta and beta measurements are nonsignificant, $p > .05$. Table 5 provides means and standard deviations for the treatment and placebo administrations for each measure.

Much of the performance data gathered on children with ADHD consists of parent and teacher checklists which produce subjective and, frequently, unreliable information. Parents and teachers do not intentionally skew their responses, but when they experience the frustrations of a typical parent or teacher and are faced with additional challenges of a high-maintenance child, there will be a tendency to respond with a greater emphasis on problem behaviors with which they must deal. Further, since the range of emotional response of a parent and teacher includes those who are dramatically expressive as well as those who de-emphasize negatives by denying to others the existence of difficulty, accuracy in parental and teacher response is elusive and unreliable. It is therefore important to derive pre- and post-test objective data on the performance of children with this diagnosis. Although CPTs do not directly measure academic performance, the utility of measuring attention, concentration and sustained focus cannot be diminished as academic performance competence depends, in large measure, on these elements. Hence there will be consequent gains in the areas of

reading, mathematics, etc. as these elements improve. Previous studies have measured significant change in CPTs with ADHD medications including methylphenidate, dexamphetamine and Adderall (which combines the neutral sulfate salts of dextroamphetamine and amphetamine with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate), but none to date have focused on non-prescriptive treatments.

The present evaluation replicated methylphenidate efficacy, as measured by CPT, but also measured the treatment value of substances not currently considered as treatment options. The design is intended not as a direct comparison of methylphenidate and the nutritional composition to each other in terms of their effectiveness in the treatment of ADHD, but rather to confirm methylphenidate efficacy compared to placebo as measured by two completely objective devices and to use the same standard comparing additional, non-prescriptive options. As parents of ADHD children search for alternative treatments, the present invention clearly provides an alternative which proves useful.

The complexity of cause and effect in the development of behavior cannot be simply studied; however, if the neuropsychological components affected by attention-deficit hyperactivity disorder can be effectively remediated, then behavioral modification can take place with appropriate and time-proven interventions.

Example 2

A nutritional composition in accordance with the present invention will be formulated as follows: A nutritional beverage mix which contains neuroactive ingredients including caffeine (120mg), choline (500mg), GABA (50mg), L-phenylalanine (500mg), and taurine (200mg), is compared against each component (caffeine, choline, GABA, L-phenylalanine, and taurine) individually in the evaluation according to the procedure of Example 1.

It will be found that the negative manifestations of ADHD, such as inattentiveness and distractibility, as measured empirically by a neuropsychological

continuous performance test and electrophysiological brain wave measures, and cognitive performance generally, is improved by the unique and synergistic combination of ingredients, compared to the results obtained with each ingredient individually.

Example 3

A nutritional composition in accordance with the present invention will be formulated as follows: A nutritional beverage mix which contains neuroactive ingredients including caffeine (120mg), choline (500mg), GABA (50mg), L-phenylalanine (500mg), taurine (200mg), L-carnitine (10mg) L-glycine (100mg), RNA (2mg), and ubiquinone (100μg), is compared against each component (caffeine, choline, GABA, L-phenylalanine, taurine, L-carnitine, L-glycine, RNA, and ubiquinone) individually in the evaluation according to the procedure of Example 1.

It will be found that the negative manifestations of ADHD, such as inattentiveness and distractibility, as measured empirically by a neuropsychological continuous performance test and electrophysiological brain wave measures, and cognitive performance generally, is improved by the unique and synergistic combination of ingredients, compared to the results obtained with each ingredient individually.

Thus it is demonstrated that the nutritional composition of the present invention provides for the improvement of cognitive performance while avoiding the use of stimulant medications, antidepressants, and/or anxiolytics, instead relying on active ingredients which have been demonstrated to have only minimal side effects or negative indications.

All patents and patent applications cited in this specification are hereby incorporated by reference as if they had been specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent to those of ordinary skill in the art in light of the disclosure that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Table 1

Mean Omission Scores by Group for Treatment (1) and Placebo (2)

	First 1/2		Second 1/2		Total	
	1	2	1	2	1	2
Nutritional Beverage (n=22)						
Mean	87.23	69.77	85.36	69.27	83.14*	67.82
SD	25.41	28.99	23.28	27.32	26.40	27.58
Methylphenidate (n=17)						
Mean	85.35	65.88	80.65	65.29	80.53*	64.41
SD	25.56	26.33	26.88	26.11	27.06	24.74

* Significantly different than placebo $p < .0001$

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Table 4
Mean Response Time Variability
Scores by Group for Treatment (1) and Placebo (2)

	First 1/2		Second 1/2		Total	
	1	2	1	2	1	2
Nutritional Beverage (n=22)						
Mean	82.23	68.36	80.64	66.09	79.95*	64.41
SD	28.29	25.47	27.86	23.21	28.73	23.43
Methylphenidate (n=17)						
Mean	85.76	69.24	84.47	64.06	84.29*	63.65
SD	22.00	23.46	23.46	22.84	23.65	23.11

* Significantly different than placebo $p < .0001$

Table 5

Mean Theta/Beta Scores by Group for Treatment (1) and Placebo (2)

	Theta		Beta	
	1	2	1	2
	Nutritional Beverage (n=22)			
Mean	10.68	11.26	2.95	3.30
SD	3.22	3.99	0.65	0.80
	Methylphenidate (n=17)			
Mean	9.63	11.79	3.59	3.57
SD	2.55	6.69	2.23	1.68

Claims:

1. A composition for improvement of cognitive performance comprising caffeine, choline, gamma aminobutyric acid, L-phenylalanine, and taurine in amounts sufficient to result in a measurable improvement in at least one physiologic parameter associated with cognitive performance.

2. A composition as recited in claim 1 comprising the following components in the indicated amounts:
approximately 60 to approximately 180 milligrams of caffeine,
approximately 250 to approximately 750 milligrams of choline,
approximately 25 to approximately 75 milligrams of gamma aminobutyric acid,
approximately 250 to approximately 750 milligrams of L-phenylalanine, and
approximately 100 to approximately 300 milligrams of taurine,
per dose.

3. A composition as recited in claim 1 comprising the following components in the indicated amounts:
approximately 96 to approximately 144 milligrams of caffeine,
approximately 400 to approximately 600 milligrams of choline,
approximately 40 to approximately 60 milligrams of gamma aminobutyric acid,
approximately 400 to approximately 600 milligrams of L-phenylalanine, and
approximately 160 to approximately 240 milligrams of taurine,
per dose.

4. A composition as recited in claim 1 in a form for oral administration.

5. A composition as recited in claim 1 in the form of a dry powder which is soluble in water.

6. A composition as recited in claim 1 in the form of an aqueous solution.

7. A composition as recited in claim 1 further comprising at least one ingredient selected from the group consisting of L-carnitine, L-glycine, ribonucleic acid, and ubiquinone.

8. A composition as recited in claim 7 wherein each selected ingredient is in the following indicated amount:
approximately 10 to approximately 15 milligrams of L-carnitine,
approximately 50 to approximately 150 milligrams of L-glycine,
approximately 1 to approximately 3 milligrams of ribonucleic acid, and
approximately 50 to approximately 150 micrograms of ubiquinone.

9. A composition as recited in claim 1 further comprising at least one ingredient selected from the group consisting of fructose, maltodextrin, citric acid, ascorbic acid, calcium pantothenate, natural flavor, Vitamin A (beta carotene, palmitate), niacinamide, Vitamin E Succinate, acesulfame, niacin, pyridoxine hydrochloride, zinc monomethionine, riboflavin, thiamin hydrochloride, copper amino acid chelate, chromium polynicotinate, and cyanocobalamin.

10. A method for treating a mammal for inducing therein a beneficial effect on at least one physiologic parameter associated with improved cognitive performance comprising administering to a mammal a composition comprising caffeine, choline, gamma aminobutyric acid, L-phenylalanine, and taurine in an amount sufficient to result in a measurable improvement in said physiological parameter.

11. A method as recited in claim 10 wherein said composition comprising the following components in the indicated amounts:
approximately 60 to approximately 180 milligrams of caffeine,
approximately 250 to approximately 750 milligrams of choline,
approximately 25 to approximately 75 milligrams of gamma aminobutyric acid,
approximately 250 to approximately 750 milligrams of L-phenylalanine, and
approximately 100 to approximately 300 milligrams of taurine,
per dose.

12. A method as recited in claim 10 wherein said composition comprising the following components in the indicated amounts:
approximately 96 to approximately 144 milligrams of caffeine,
approximately 400 to approximately 600 milligrams of choline,
approximately 40 to approximately 60 milligrams of gamma aminobutyric acid,
approximately 400 to approximately 600 milligrams of L-phenylalanine, and
approximately 160 to approximately 240 milligrams of taurine,
per dose.

13. A method as recited in claim 10 wherein said composition is in a form for oral administration.

14. A method as recited in claim 10 wherein said composition is in the form of a dry powder which is soluble in water.

15. A method as recited in claim 10 wherein said composition is in the form of an aqueous solution.

16. A method as recited in claim 10 wherein said composition further comprising at least one ingredient selected from the group consisting of L-carnitine, L-glycine, ribonucleic acid, and ubiquinone.

17. A method as recited in claim 16 wherein each selected ingredient of said composition is in the following indicated amount:
approximately 10 to approximately 15 milligrams of L-carnitine,
approximately 50 to approximately 150 milligrams of L-glycine,
approximately 1 to approximately 3 milligrams of ribonucleic acid, and
approximately 50 to approximately 150 micrograms of ubiquinone.

18. A method as recited in claim 10 wherein said composition further comprising at least one ingredient selected from the group consisting of fructose, maltodextrin, citric acid, ascorbic acid, calcium pantothenate, natural flavor, Vitamin A (beta carotene, palmitate), niacinamide, Vitamin E Succinate, acesulfame, niacin, pyridoxine hydrochloride, zinc monomethionine, riboflavin, thiamin hydrochloride, copper amino acid chelate, chromium polynicotinate, and cyanocobalamin.

INTERNATIONAL SEARCH REPORT	International application No. PCT/US00/10482

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 47/00, 31/13, 31/24, 31/52
US CL : 424/439; 514/263, 538, 645
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/439; 514/263, 538, 645

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS MEDLINE BIOSIS
search terms: cognitive, caffeine, choline gamma aminobutyric acid, phenylalanine, taurine, hyperactive disorder

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,837,730 A (JAVITT) 17 November 1998, Abstract.	7-8, 16-17
Y	US 5,571,441 A (ANDON et al) 05 November 1996, abstract, col. 3, lines 60-67, col. 5, lines 25-42, col. 6, lines 19-32, col 2, 32-39.	1-18
Y	STOLL et al. Choline in the Treatment of Rapid-Cycling Bipolar Disorder: Clinical and Neurochemical Finding in Lithium-Treated Patients. Biol. Psychiatry 1996, Vol 40, page 382-388, entire document.	1-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 JUNE 2000	02 AUG 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/10482

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database Medline on STN, US National Library of Medicine, (Bethesda, MD, USA), No. 98343650, WENDER, P.H. 'Pharmacotherapy of attention-deficit/hyperactivity disorder in adults,' abstract, Journal of Clinical Psychiatry, 1998, 59, Suppl 7, 76-9.	1-18
Y	Database Medline on STN, US National Library of Medicine, (Bethesda, MD, USA), No. 75092533, MONTANINI et al. 'Taurine in the treatment of diffuse cerebral arteriopathies. Clinical and electroencephalographic observations and psychological tests,' abstract, Clinica Therapeutica. 15 December 1974, Vol. 71 No. 5, 427-39 (Italian).	1-18